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Formoterol Turbuhaler® for as-needed therapy in patients with mild acute exacerbations of COPD

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Abstract Worsening of underlying bronchospasm may be associated with acute exacerbations of chronic obstructive pulmonary disease (COPD). As airway obstruction becomes more severe, the therapeutic option is to add a short-acting inhaled β_2-agonist as needed to cause rapid relief of bronchospasm. Unfortunately, however, the most effective dosage may increase above that recommended during acute exacerbations. Formoterol (Oxis®) Turbuhaler® has a rapid onset of action (within minutes) and demonstrates a maintained effect on airway function. In this study, we examined the effects of formoterol used as needed in 20 patients with acute exacerbations of COPD. A dose–response curve to inhaled formoterol (9 μg per inhalation) or placebo was constructed using three separate inhalations, i.e. a total cumulative dose of 27 μg. Dose increments were given at 20-min intervals, with measurements being made 15 min after each dose. Formoterol, but not placebo, induced a large and significant ($P < 0{\cdot}001$) dose-dependent increase in forced expiratory volume in 1 sec (FEV_1) [mean differences from baseline = 0·131 l after 9 μg formoterol (95% CI: 0·096–0·167)] 0·181 l after 18 μg formoterol (95% CI: 0·140–0·222 l) and 0·208 l after 27 μg formoterol (95% CI: 0·153–0·263 l). However, 27 μg formoterol did not induce further benefit [0·027 l (95% CI: −0·008–0·062 l); $P = 0{\cdot}121$] when compared with 18 μg formoterol. Results of this study suggest the use of higher than customary dose of formoterol for as-needed therapy to provide rapid relief of bronchospasm in patients suffering from acute exacerbations of partially reversible COPD.

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INTRODUCTION

Acute exacerbations of chronic obstructive pulmonary disease (COPD) may result in deterioration of the underlying bronchospasm. This worsened airflow obstruction may be reversed in some patients by the use of bronchodilators (1). Although the amount of reversibility achieved may be relatively small, any improvement in airflow could be extremely important in the management of these patients (2).

For increased airway obstruction, the therapeutic option is to add a short-acting inhaled β_2-agonist, such as salbutamol or terbutaline, for rapid relief of bronchospasm (3,4). A small number of studies suggest that inhaled β_2-agonists, as a class, are of benefit in exacerbations of COPD, showing improvements in forced expiratory volume in 1 sec (FEV_1) and in dyspnoea scores (5). Substantial incremental increase in FEV_1 in response to increasing doses of β-agonists beyond those commonly used in clinical practice is restricted to a minority of patients (6), however, the maximal effective dose of short-acting, inhaled β_2-agonists in COPD exacerbations is not known. The optimal dosage might be greater than the conventional one (7).

Barclay *et al.* (8) have demonstrated that several COPD patients were not responsive to 200 μg inhaled salbutamol, but they obtained some degree of bronchodilation when the dose of inhaled salbutamol was gradually increased. Other studies have reported similar findings (9,10). Data from studies of COPD exacerbations indicate that 3–4 puffs of β_2-agonists produce significant (18–22%) levels of bronchodilation (11,12). Lloberes *et al.* (12) showed that, in at least half of the patients, the dose of salbutamol that produced the maximal bronchodilation was twice that currently employed. The functional duration of effect of short-acting inhaled β_2-agonists is decreased in COPD exacerbation (13).

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Therefore, because of the severity of illness, β_2-agonists should be titrated to maximal effect whenever possible (14). Thus, if 3–4 puffs every 4 h have not been effective, short-acting inhaled β_2-agonists should be administered by 3–4 puffs every 1–2 h, if tolerated, until clinical improvement occurs. The American Thoracic Society (ATS) recommendation for severe COPD exacerbation is 6–8 puffs every 2 h (4). Generally, the maximum bronchodilator response to inhaled β_2-agonists in COPD occurs significantly later to that observed in asthmatics; however, it is possible to obtain 80% of the maximum bronchodilator response quite rapidly (15).

β_2-agonists with long-lasting effects (formoterol and salmeterol) have also been developed and offer an interesting new therapeutic option for COPD. However, at present, their role in COPD treatment is still being debated (16).

Formoterol has been shown to produce dose-proportional bronchodilation in patients with partially reversible obstructive airway disease (17): the onset of action of formoterol is as rapid as both salbutamol and terbutaline (18,19), and a significant effect occurs with formoterol within minutes of inhalation of a therapeutic dose (20). Formoterol administered to patients with moderate asthma at different single doses (delivered doses of 4·5, 9, 18 or 27 μg), via a specific device (Turbuhaler®), induced at least a 50% increase in specific airways conductance (sGaw) within 1–4 min (21). Formoterol induces a prolonged bronchodilation (approximately 12 h) in partially reversible severe COPD (17,22) and, administered via Turbuhaler®, it causes long-lasting improvements in lung function in apparently poorly reversible COPD (23).

In consideration of the fast onset of action exhibited by formoterol, we have investigated the acute bronchodilating effect of cumulative doses of this drug administered via Turbuhaler® in patients with acute exacerbations of COPD to determine if this drug might be used for as-needed therapy in this condition.

METHODS

Study design

This was a randomized, double-blind, cross-over study taking place over two consecutive days. All work was conducted according to the rules of the Declaration of Helsinki and was approved by an independent scientific ethics committee.

Patients

Patients attending outpatient clinics with acute exacerbation of COPD, and who were willing to participate, were recruited. The diagnosis of COPD was consistent with the diagnostic standards of British Thoracic Society (BTS) guidelines for the management of COPD (24). Acute exacerbation was defined as a sustained worsening of the patient's condition from the stable state and beyond normal day-to-day variations: that is, acute in onset and necessitating a change in regular medication in a patient with underlying COPD (25). All patients had no indication for hospitalization, according to the BTS guidelines (24). The protocol of this study included a placebo treatment. For this reason, due to ethical reasons, all patients were suffering from only a mild, acute exacerbation of COPD. Exacerbations were defined as mild because each patient had an increased need for medication, which he/she was able to manage in his/her own normal environment (25). Table 1 outlines the baseline characteristics of the population studied.

A bronchodilator response prior to entry into the study was not required. Patients with a history of asthma, allergic rhinitis, atopy, or with a total blood eosinophil count over 400 mm^{-3} were excluded. Patients were also excluded if they had co-morbidities (such as congestive heart failure or pulmonary embolus) or complications of COPD (e.g. pneumothorax) as the aetiology of exacerbation of their symptoms. No patient was suffering from febrile tracheobronchitis.

Additional medication

Oral bronchodilators were not permitted during the study. Inhaled short-acting bronchodilator drugs, and other inhaled long-acting bronchodilator agents, were not permitted for at least 12 h and 24 h prior to each test, respectively. Short-acting β_2-agonists were permitted soon after each test when required. All patients received a treatment with an oral antibiotic (co-amoxiclav or levofloxacin) and an inhaled steroid (budesonide 400 μg twice daily).

Patients were asked not to consume cola drinks, coffee or tea and not to smoke in the hours before and during the investigation.

Treatment

A dose–response curve to formoterol 9 μg per inhalation (Oxis, AstraZeneca, Milan, Italy) or placebo, both administered via Turbuhaler®, was constructed using three separate inhalations, i.e. a total cumulative delivered dose of 27 μg formoterol. After baseline measurements, dose increments were given at 20-min intervals, with measurements being made 15 min after each dose. Spirometric testing was performed according to the procedures described in the ATS 1987 update (26). Three acceptable forced expiratory manoeuvres were performed in order to obtain two reproducible results for forced vital capacity (FVC) and FEV_1. The highest FVC and FEV_1, obtained from one or other of the reproducible› curves, were kept for analysis.

Table 1. Anthropometric data and pulmonary function of patients

Patient	Sex	Age (yrs)	Height (cm)	FEV_1 (l)	FEV_1 (% predicted)	FVC (l)	FVC (% predicted)	Anthonisen-type exacerbation
1	M	61	164	0·65	23	1·05	30	II
2	M	65	165	0·61	22	1·28	37	II
3	F	54	170	1·40	50	2·01	62	I
4	M	69	181	1·43	43	2·12	50	I
5	M	65	163	1·69	64	2·35	70	I
6	M	67	165	1·53	58	2·00	59	II
7	M	86	165	1·03	49	1·65	57	II
8	M	67	172	1·39	47	1·94	51	I
9	M	71	169	1·69	62	2·31	65	II
10	M	61	160	1·32	50	2·09	64	I
11	M	59	168	1·24	41	1·74	46	II
12	M	62	167	0·51	18	0·90	25	II
13	M	65	164	1·00	37	1·26	37	I
14	M	73	160	1·26	55	1·50	50	II
15	M	63	169	1·08	37	2·12	57	II
16	M	75	185	1·52	46	2·11	48	II
17	M	72	161	0·67	28	1·46	48	II
18	M	55	161	0·48	17	1·27	36	I
19	M	83	176	2·64	61	2·59	71	I
20	M	78	160	0·93	52	1·47	68	II

Analysis of data

Spirometric data for each treatment were analysed using the Student's *t*-test for paired variables. Mean responses were also compared by multi-factorial analysis of variance (ANOVA) to establish any significant overall effect between the two treatments. In the presence of a significant overall ANOVA, Duncan's multiple range testing with 95% confidence limits was used to identify where differences were significant. A probability level of $P < 0{\cdot}05$ was considered as significant for all tests.

RESULTS

Twenty patients were enrolled and all completed the 2-day study. Significant differences occurred between the baseline spirometric values of the two treatment groups for FEV_1 [mean difference = 0·047 l (95% CI: 0·006–0·088 l); $P = 0{\cdot}027$], but not for FVC [mean difference = 0·032 l (95% CI: −0·014–0·078 l); $P = 0{\cdot}161$]. Apparently, no carry-over effect was detectable. In fact, in the 10 patients who received formoterol as first and placebo as second, the mean baseline FEV_1 values were 1·237 l (95% CI: 0·940–1·534 l) and 1·067 l (95% CI: 0·816–1·318 l), respectively, whereas in the 10 patients who received placebo as first and formoteral as second, the mean baseline FEV_1 values were 1·217 l (95% CI: 0·940–1·494 l) and 1·141 (95% CI: 0·860–1·422 l), respectively.

Improvements in FEV_1 and FVC with each cumulative dose of formoterol were highly significant compared with placebo ($P = 0{\cdot}001$). The mean changes in FEV_1 and FVC from control baseline values for each treatment are shown in Fig. 1.

Formoterol, but not placebo, induced large and significant ($P < 0{\cdot}001$) dose-dependent increases in FEV_1 and FVC. For FEV_1 mean differences from baseline were 0·131 l after 9 μg formoterol (95% CI: 0·096–0·167 l), 0·181 l after 18 μg formoterol (95% CI: 0·140–0·222 l) and 0·208 l after 27 μg formoterol (95% CI: 0·153–0·263 l). For FVC, mean differences from baseline were 0·169 l after 9 μg formoterol (95% CI: 0·073–0·265 l), 0·236 l after 18 μg formoterol (95% CI: 0·159–0·313 l) and 0·292 l after 27 μg formoterol (95% CI: 0·142–0·254 l). However, 27 μg formoterol did not induce further significant improvement in FEV_1 [0·027 l (95% CI: −0·008–0·062 l); $P = 0{\cdot}121$; 0·057 l (95% CI: −0·031–0·144 l); $P = 0{\cdot}193$] when compared with 18 μg formoterol. It is interesting to note that the mean percentage increase from baseline in inspiratory capacity (IC), an index of hyperinflation, after 27 μg formoterol was lower than that in FVC (9·7% and 16·7%, respectively).

In effect, 18 μg formoterol induced a higher bronchodilation than did 27 μg formoterol in six out of 20 patients,

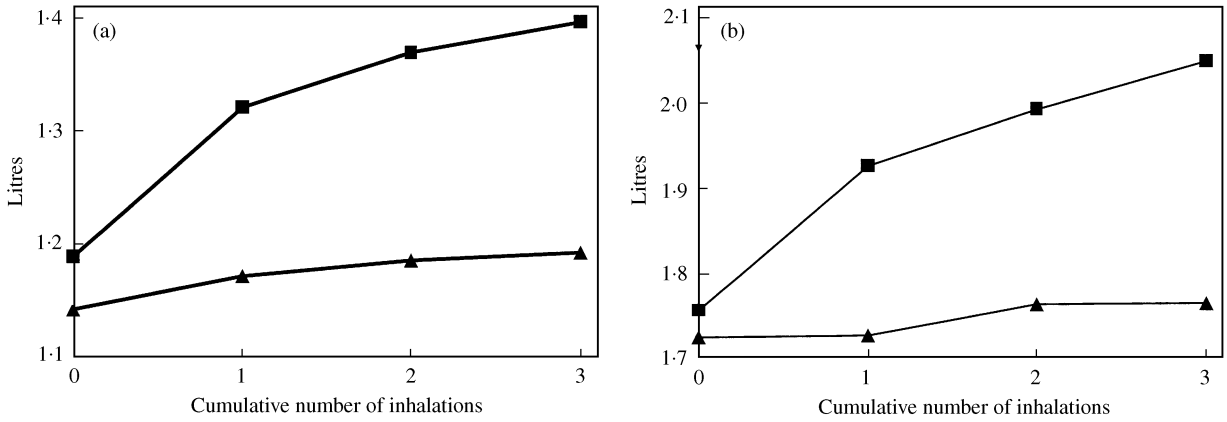

Fig. 1. Mean (a) FEV_1 and (b) FVC changes from control baseline values for formoterol (9 μg per inhalation) (■) and placebo (▲).

and produced at least 80% of the bronchodilator response evoked by the highest dose of formoterol in another five patients. After inhalation of 27 μg formoterol Turbuhaler®, 75% of the patients showed an absolute increase in FEV_1 of at least 160 ml. This cut-off for excluding errors was used due to the known coefficient of variation of spirometry in patients with COPD (1). After 18 μg formoterol, 65% of the patients showed this increase.

No patient complained of adverse symptoms (e.g. palpitations or significantly increased heart rate) during the study. Moreover, no patient significantly worsened after these two days; consequently, no hospital admission was necessary.

DISCUSSION

This study shows that formoterol Turbuhaler® induces a rapid and significant bronchodilation and can be used for as-needed medication in many patients with acute exacerbations of COPD. A delivered dose of 18 μg formoterol (24 μg metered dose) seems to induce clinically relevant effect in these patients. However, since 70% of patients examined in this investigation benefited by the highest used dose of formoterol, it is advisable to administer a cumulative 27 μg delivered dose of formoterol for as-needed medication. This will cause rapid relief of bronchospasm in patients with acute exacerbation of COPD, in agreement with the dose–response relationship found for the increase from baseline in sGaw soon after inhalation (21).

Although long-acting β_2-agonists are currently not approved for use in exacerbations of COPD and we know little about their duration of action in this condition, their long-lasting effect is important. This is particularly true when these drugs have a rapid onset of action, similar to short-acting β_2-agonists. These characteristics might allow for both good relief of symptoms and also prolonged control. This means that repeat doses should not normally be needed.

In this study, formoterol was administered via Turbuhaler®. This contrasts with the Veteran Health Administration clinical practice guideline for the management of COPD that strongly encourages use of spacers in COPD exacerbation (27). The addition of a spacer device, however, may increase the variability of the available dose (28).

Tönnesen *et al.* (29) demonstrated that inhalation of terbutaline via Turbuhaler® produced a significantly greater increase in FEV_1 compared with the same dose of the β_2-agonist administered via a conventional, chlorofluorocarbon inhaler and Nebuhaler® (750 ml spacer) in patients attending the emergency department with acute severe bronchial obstruction. Another study showed that the same bronchodilating effect could be achieved when half the dose of salbutamol normally given via a conventional pressurized metered dose inhaler (pMDI) is given via Turbuhaler® in patients with reversible airway obstruction (30). These findings are not a surprise because Turbuhaler® delivers about twice the amount of drug to the lungs as the pMDI and the observed difference in deposition is reflected in the bronchodilating effect (31). However, some studies indicate that the dry-powder capsule inhaler and pMDI formulations of formoterol are equipotent in bronchodilation (18,32).

CONCLUSION

This study suggests the use of higher than customary dose of formoterol for as-needed medication in patients suffering from acute exacerbations of partially reversible COPD. Studies in a larger population will determine if the functional duration of effect of formoterol is decreased in COPD exacerbations, as occurs with short-acting β_2-agonists.

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